Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=AND			
L12	L11 and (treatment or therapy)	17	L12
L11	L5 same (cancer or tumor or tumour)	18	L11
L10	L7 and (gene (w) therapy)	21	L10
L9	L8 and (methotrexate or edatrexate or aminopterin)	9	L9
L8	L7 and (vector or plasmid)	33	L8
L7	L5 and (cancer or tumor or tumour or neoplastic)	65	L7
L6	L5 same (DNA or RNA or vector or plasmid)	22	L6
L5	(FPGS or (Folylpolyglutamyl adj synthetase))	610	L5
L4	L2 and (antifolate or (folate adj antagonist))	0	L4
L3	L2 and (FPGS)	0	L3
L2	Breakefield-xandra-o$.in.	23	L2
L1	Aghi-manish.in.	0	L1

END OF SEARCH HISTORY

Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The *gene* encoding *folylpolyglutamyl* *synthetase* (FPGS) was assigned to mouse chromosome 2 by complementation mapping. Chinese hamster ovary cells (AuxB1) deficient in FPGS, and consequently auxotrophic for glycine, adenosine, and...

```
?ds

Set     Items   Description
S1          0   (FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (ANTIFOLATE (W) DRUG)
S2          0   (FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (CANCER OR TUMOR OR -
              TUMOUR OR NEOPLASTIC)
S3          0   (FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (ANTIFOLATE (W) DRU-
              G)
S4         15   (FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (CANCER OR TUMOR OR
              TUMOUR OR NEOPLASTIC)
S5          2   S4 AND (VECTOR)
S6          1   RD (unique items)
S7          9   RD S4 (unique items)
S8          5   (FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (GENE OR CDNA)
S9          3   RD (unique items)
?s (human (w) folylpolyglutamyl (w) synthetase)
       8653581  HUMAN
            23  FOLYLPOLYGLUTAMYL
         30952  SYNTHETASE
    S10      0  (HUMAN (W) FOLYLPOLYGLUTAMYL (W) SYNTHETASE)
?s (folypolyglutamyl (w) synthetase) and (DNA or genomic)
            2  FOLYPOLYGLUTAMYL
         30952  SYNTHETASE
            0  FOLYPOLYGLUTAMYL(W)SYNTHETASE
        838677  DNA
         72742  GENOMIC
    S11      0  (FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (DNA OR GENOMIC)
?ds

Set     Items   Description
S1          0   (FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (ANTIFOLATE (W) DRUG)
S2          0   (FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (CANCER OR TUMOR OR -
              TUMOUR OR NEOPLASTIC)
S3          0   (FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (ANTIFOLATE (W) DRU-
              G)
S4         15   (FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (CANCER OR TUMOR OR
              TUMOUR OR NEOPLASTIC)
S5          2   S4 AND (VECTOR)
S6          1   RD (unique items)
S7          9   RD S4 (unique items)
S8          5   (FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (GENE OR CDNA)
S9          3   RD (unique items)
S10         0   (HUMAN (W) FOLYLPOLYGLUTAMYL (W) SYNTHETASE)
S11         0   (FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (DNA OR GENOMIC)
?logoff
       31jan02 17:03:09 User259876 Session D313.2
            $4.13    1.290 DialUnits File155
               $2.00  10 Type(s) in Format  3
            $2.00  10 Types
     $6.13  Estimated cost File155
            $1.83    0.622 DialUnits File159
               $0.75  3 Type(s) in Format  3
            $0.75  3 Types
     $2.58  Estimated cost File159
            OneSearch, 2 files,  1.912 DialUnits FileOS
     $0.60  TYMNET
     $9.31  Estimated cost this search
     $9.63  Estimated total session cost   2.001 DialUnits
```

```
### Status: Path 1 of [Dialog Information Services via Modem]

### Status: Initializing TCP/IP using (UseTelnetProto 1 ServiceID pto-dialog)
Trying 3106900061...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ******** HHHHHHHH SSSSSSSS?
### Status: Signing onto Dialog
 ********
ENTER PASSWORD:
 ******** HHHHHHHH SSSSSSSS? ********
Welcome to DIALOG
### Status: Connected


Dialog level 02.01.23D

Last logoff:  28jan02 11:32:51
Logon file001 31jan02 16:51:14
           *** ANNOUNCEMENT ***
                    ***
--Connect Time joins DialUnits as pricing
options on Dialog.  See HELP CONNECT for
information.
                    ***
--SourceOne patents are now delivered to your
email inbox as PDF replacing TIFF delivery.
See HELP SOURCE1 for more information.
                    ***
--Important news for public and academic
libraries.  See HELP LIBRARY for more information.
                    ***
--Important Notice to Freelance Authors--
See HELP FREELANCE for more information
                    ***
NEW FILES RELEASED
***TEME - Technology and Management(File 95)
***NewsRx Weekly Reports (File 135)
***TRADEMARKSCAN-Japan (File 669)
***Financial Times Fulltext (File 476)
                    ***
UPDATING RESUMED
***Delphes European Business (File 481)
                    ***
RELOADED
***CLAIMS/US PATENTS (Files 340, 341, 942)
***Kompass Middle East/Africa/Mediterranean (File 585)
***Kompass Asia/Pacific (File 592)
***Kompass Central/Eastern Europe (File 593)
***Kompass Canada (File 594)
***CANCERLIT (File 159)
***D&B - Dun's Market Identifiers  (516)
***Information Science Abstracts (File 202)

REMOVED
***Tax Notes Today (File 790)
***State Tax Today (File 791)
***Worldwide Tax Daily (File 792)
***Court Filings (File 793)

***New document supplier***
IMED has been changed to INFOTRIE (see HELP OINFOTRI)
```

```
>>>Get immediate news wi[redacted]Dialog's First Release
   news service.  First Release updates major newswire
   databases within 15 minutes of transmission over the
   wire.  First Release provides full Dialog searchability
   and full-text features.  To search First Release files in
   OneSearch simply BEGIN FIRST for coverage from Dialog's
   broad spectrum of news wires.

     >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
     >>>    of new databases, price changes, etc.      <<<
                    ****
KWIC is set to 50.
HILIGHT set on as '*'
****                                    ****

File   1:ERIC  1966-2002/Jan 11
       (c) format only 2002 The Dialog Corporation

      Set  Items  Description
      ---  -----  -----------
Cost is in DialUnits
?b 155, 159
       31jan02 16:51:30 User259876 Session D313.1
            $0.31    0.090 DialUnits File1
     $0.31  Estimated cost File1
     $0.01  TYMNET
     $0.32  Estimated cost this search
     $0.32  Estimated total session cost   0.090 DialUnits


SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2002/Jan W1
  File 159:Cancerlit  1975-2001/Oct
        (c) format only 2001 Dialog Corporation
*File 159: File temporarily is not updating.  Updating expected to
resume in March 2002.

      Set  Items  Description
      ---  -----  -----------
?s (folypolyglutamyl (w) synthetase) and (antifolate (w) drug)
              2  FOLYPOLYGLUTAMYL
          30952  SYNTHETASE
              0  FOLYPOLYGLUTAMYL(W)SYNTHETASE
           1559  ANTIFOLATE
        2759678  DRUG
             66  ANTIFOLATE(W)DRUG
      S1      0  (FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (ANTIFOLATE (W)
                 DRUG)
?s (folypolyglutamyl (w) synthetase) and (cancer or tumor or tumour or neoplastic)
              2  FOLYPOLYGLUTAMYL
          30952  SYNTHETASE
              0  FOLYPOLYGLUTAMYL(W)SYNTHETASE
         716624  CANCER
         941406  TUMOR
         139266  TUMOUR
         157470  NEOPLASTIC
      S2      0  (FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (CANCER OR TUMOR OR
                 TUMOUR OR NEOPLASTIC)
?s (folylpolyglutamyl (w) synthetase) and (antifolate (w) drug)
             23  FOLYLPOLYGLUTAMYL
          30952  SYNTHETASE
             18  FOLYLPOLYGLUTAMYL(W)SYNTHETASE
           1559  ANTIFOLATE
        2759678  DRUG
             66  ANTIFOLATE(W)DRUG
      S3      0  (FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (ANTIFOLATE (W)
```

DRUG)
?s (folylpolyglutamyl (w) synthetase) and (cancer or tumor or tumour or neoplastic)
23 FOLYLPOLYGLUTAMYL
30952 SYNTHETASE
18 FOLYLPOLYGLUTAMYL(W)SYNTHETASE
716624 CANCER
941406 TUMOR
139266 TUMOUR
157470 NEOPLASTIC
S4 15 (FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (CANCER OR TUMOR OR TUMOUR OR NEOPLASTIC)
?s s4 and (vector)
15 S4
53515 VECTOR
S5 2 S4 AND (VECTOR)
?rd
...completed examining records
S6 1 RD (unique items)
?t s6/3,k/all

6/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10806665 99341974 PMID: 10413425
***Folylpolyglutamyl* *synthetase* gene transfer and glioma antifolate sensitivity in culture and in vivo.**
Aghi M; Kramm CM; Breakefield XO
Department of Neurology, Massachusetts General Hospital, Boston, MA, USA.
Journal of the National Cancer Institute (UNITED STATES) Jul 21 1999, 91 (14) p1233-41, ISSN 0027-8874 Journal Code: J9J
Contract/Grant No.: P30CA69246, CA, NCI
Comment in J Natl Cancer Inst. 1999 Dec 1;91(23) 2047-50; Comment in J Natl Cancer Inst. 1999 Jul 21;91(14):1178-9
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

***Folylpolyglutamyl* *synthetase* gene transfer and glioma antifolate sensitivity in culture and in vivo.**
... against slow-growing tumors and are toxic to actively replicating cells in normal tissues. These drugs are converted intracellularly into polyglutamate derivatives by the enzyme *folylpolyglutamyl* *synthetase* (FPGS). Because tumors with high expression of FPGS often respond to nontoxic antifolate doses, we investigated whether augmenting tumoral FPGS activity by gene delivery would...

...ability to increase the chemosensitivity of nearby nontransfected cells, i.e., a bystander effect. The antifolate sensitivity of nonselected cells transduced with a hybrid amplicon *vector* that expressed FPGS was also ascertained. RESULTS: In comparison with 9L cells, 9L/FPGS cells displayed enhanced sensitivity to 4-hour pulses of antifolate. Subcutaneous...

...rodent and human glioma cell lines, including one with high pre-existing FPGS activity, and in canine and human glioblastoma cell lines.transduced with a *vector* bearing FPGS cDNA. CONCLUSIONS: FPGS gene delivery enhances the antifolate sensitivity of several glioma cell lines and merits further evaluation as a therapeutic strategy.
...; pharmacology--PD; Chromatography, Thin Layer; Dogs; Dose-Response Relationship, Drug; Glioma; Neoplasms--enzymology--EN; Neoplasms--genetics --GE; Peptide Synthases--metabolism--ME; Rats; Transduction, Genetic; Transfection; *Tumor* Cells, Cultured
?ds

Set	Items	Description
S1	0	(FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (ANTIFOLATE (W) DRUG)
S2	0	(FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (CANCER OR TUMOR OR -

TUMOUR OR NEOPLASTIC)
S3 0 (FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (ANTIFOLATE (W) DRUG)
S4 15 (FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (CANCER OR TUMOR OR TUMOUR OR NEOPLASTIC)
S5 2 S4 AND (VECTOR)
S6 1 RD (unique items)
?rd s4
...completed examining records
S7 9 RD S4 (unique items)
?t s7/3,k/all

7/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10806665 99341974 PMID: 10413425
***Folylpolyglutamyl* *synthetase* gene transfer and glioma antifolate sensitivity in culture and in vivo.**
Aghi M; Kramm CM; Breakefield XO
Department of Neurology, Massachusetts General Hospital, Boston, MA, USA.
Journal of the National Cancer Institute (UNITED STATES) Jul 21 1999, 91 (14) p1233-41, ISSN 0027-8874 Journal Code: J9J
Contract/Grant No.: P30CA69246, CA, NCI
Comment in J Natl Cancer Inst. 1999 Dec 1;91(23) 2047-50; Comment in J Natl Cancer Inst. 1999 Jul 21;91(14):1178-9
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

***Folylpolyglutamyl* *synthetase* gene transfer and glioma antifolate sensitivity in culture and in vivo.**
... against slow-growing tumors and are toxic to actively replicating cells in normal tissues. These drugs are converted intracellularly into polyglutamate derivatives by the enzyme *folylpolyglutamyl* *synthetase* (FPGS). Because tumors with high expression of FPGS often respond to nontoxic antifolate doses, we investigated whether augmenting tumoral FPGS activity by gene delivery would...
...; pharmacology--PD; Chromatography, Thin Layer; Dogs; Dose-Response Relationship, Drug; Glioma; Neoplasms--enzymology--EN; Neoplasms--genetics --GE; Peptide Synthases--metabolism--ME; Rats; Transduction, Genetic; Transfection; *Tumor* Cells, Cultured

7/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10770844 20048020 PMID: 10580033
Re: *Folylpolyglutamyl* *synthetase* gene transfer and glioma antifolate sensitivity in culture and in vivo.
Jansen G; Peters GJ; Pinedo HM; Priest DG; Assaraf YG
Journal of the National Cancer Institute (UNITED STATES) Dec 1 1999, 91 (23) p2047-50, ISSN 0027-8874 Journal Code: J9J
Comment on J Natl Cancer Inst. 1999 Jul 21;91(14) 1178-9; Comment on J Natl Cancer Inst. 1999 Jul 21;91(14):1233-41
Languages: ENGLISH
Document type: Comment; Letter
Record type: Completed

Re: *Folylpolyglutamyl* *synthetase* gene transfer and glioma antifolate sensitivity in culture and in vivo.
; Gene Transfer Techniques; Glioma--enzymology--EN; *Tumor* Cells, Cultured

7/3,K/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10358072 99427978 PMID: 10499632

Impact of polyglutamation on sensitivity to raltitrexed and methotrexate in relation to drug-induced inhibition of de novo thymidylate and purine biosynthesis in CCRF-CEM cell lines.

Barnes MJ; Estlin EJ; Taylor GA; Aherne GW; Hardcastle A; McGuire JJ; Calvete JA; Lunec J; Pearson AD; Newell DR

Cancer Research Unit, University of Newcastle, Newcastle upon Tyne, United Kingdom.

Clinical cancer research (UNITED STATES) Sep 1999, 5 (9) p2548-58, ISSN 1078-0432 Journal Code: C2H

Contract/Grant No.: CA16056, CA, NCI; CA43500, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The aim of this study was to investigate the influence of *folylpolyglutamyl* *synthetase* (FPGS) activity on the cellular pharmacology of the classical antifolates raltitrexed and methotrexate (MTX) using two human leukemia cell lines, CCRF-CEM and CCRF-CEM...

...; PK; RNA, Messenger--metabolism--ME; Thiophenes--metabolism--ME; Thiophenes--pharmacokinetics--PK; Thymidine Monophosphate--biosynthesis --BI; Thymidylate Synthase--antagonists and inhibitors--AI; Thymidylate Synthase--metabolism--ME; *Tumor* Cells, Cultured

7/3,K/4 (Item 4 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

06958861 90315629 PMID: 2369741

Differing specificities for 4-aminofolate analogues of *folylpolyglutamyl* *synthetase* from tumors and proliferative intestinal epithelium of the mouse with significance for selective antitumor action.

Rumberger BG; Barrueco JR; Sirotnak FM

Memorial Sloan Kettering Cancer Center, New York, New York 10021.

Cancer research (UNITED STATES) Aug 1 1990, 50 (15) p4639-43, ISSN 0008-5472 Journal Code: CNF

Contract/Grant No.: CA08748, CA, NCI; CA18856, CA, NCI; CA22764, CA, NCI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Differing specificities for 4-aminofolate analogues of *folylpolyglutamyl* *synthetase* from tumors and proliferative intestinal epithelium of the mouse with significance for selective antitumor action.

Folylpolyglutamyl *synthetase* (FPGS), partially purified from murine L1210 leukemia and Sarcoma 180 cells and the proliferative fraction of luminal epithelium from mouse small intestine (the site of limiting toxicity to folate analogues), was examined for its ability to utilize various 4-aminofolates as substrates. For *tumor*-derived FPGS, aminopterin was the most preferred substrate overall, exhibiting the lowest value for apparent Km and highest Vmax. The other analogues and folic acid...

...intestinal epithelium, aminopterin was also the preferred substrate, but the value for Vmax (derived with crude cell-free extract) was 6-fold lower than for *tumor* cell FPGS. Values for Vmax (derived with partially purified FPGS) for the other 4-aminofolate analogues and folic acid were similar (methotrexate) or 2-fold...

...10-deazaaminopterin) and 5-fold (folic acid) lower than for aminopterin. The value for Km derived with aminopterin was similar to that derived for either *tumor* cell FPGS. The value for folic acid was 2-fold higher, and alkylation of aminopterin (methotrexate) or carbon to nitrogen substitution (10-deazaaminopterin) at N...

7/3,K/5 (Item 5 fro ile: 155)
DIALOG(R)File 155:MEDLINE(R)

06092386 85151788 PMID: 3978616
Similar differential for total polyglutamylation and cytotoxicity among various folate analogues in human and murine *tumor* cells in vitro.
Samuels LL; Moccio DM; Sirotnak FM
Cancer research (UNITED STATES) Apr 1985, 45 (4) p1488-95, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: CA 08748, CA, NCI; CA 18856, CA, NCI; CA 22346, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Similar differential for total polyglutamylation and cytotoxicity among various folate analogues in human and murine *tumor* cells in vitro.
... analogues, methotrexate, aminopterin, 10-deazaminopterin, and 10-ethyl-10-deazaaminopterin were assessed for their ability to be metabolized to poly-gamma-glutamyl derivatives in three *tumor* lines which vary in their sensitivity to these agents. Cytotoxicity of the four analogues against the murine L1210 leukemia and the human Manca B cell...

... cell types. Initial rates of polyglutamate accumulation of the four analogues, which were determined under conditions of comparable rates of drug entry into the three *tumor* cell lines, were 7- to 18-fold less than drug entry rates. In L1210 and Sarcoma 180 cells, the relative rates of polyglutamylation were in...

... polyglutamylation in Manca cells were in the order 10-ethyl-10-deazaaminopterin approximately equal to aminopterin greater than 10-deazaaminopterin greater than methotrexate, suggesting that *folylpolyglutamyl* *synthetase* may have varying substrate preferences in different cell types. The maximum relative extents of total polyglutamate accumulation in L1210 cells were 85 to 95% of...
; Aminopterin--analogs and derivatives--AA; Cells, Cultured; Kinetics; Leukemia L1210--metabolism--ME; Mice; *Tumor* Stem Cell Assay

7/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04909399 84289499 PMID: 6206061
A methotrexate-resistant human breast *cancer* cell line with multiple defects, including diminished formation of methotrexate polyglutamates.
Cowan KH; Jolivet J
Journal of biological chemistry (UNITED STATES) Sep 10 1984, 259 (17) p10793-800, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

A methotrexate-resistant human breast *cancer* cell line with multiple defects, including diminished formation of methotrexate polyglutamates.
Methotrexate (MTX)-resistant human breast *cancer* cells (MTXR ZR-75) were obtained following serial passage of the wild-type ZR-75-1 cells (wild-type ZR-75) in MTX. The resistant...

... a vast excess of free intracellular drug in these cells. This defect is not associated with any apparent change in the activity of the enzyme *folylpolyglutamyl* *synthetase* , nor is there any alteration in the apparent Km of this enzyme for MTX in the resistant cells. Further studies demonstrate that the MTXR ZR...

7/3,K/7 (Item 1 from file: 159)

DIALOG(R)File 159:Cancer

01409429 98642952

Predictors of response and toxicity in patients with advanced colorectal *cancer* (CRC) treated with Tomudex (Meeting abstract).

Inst. of Cancer Res. and Royal Marsden Trust, Sy, UK

Proc Annu Meet Am Soc Clin Oncol; 16 1997 ISSN 0732-183X
Languages: ENGLISH
Document Type: MEETING ABSTRACTS; CLINICAL TRIAL; CLINICAL TRIAL, PHASE II
Record type: Completed

Predictors of response and toxicity in patients with advanced colorectal *cancer* (CRC) treated with Tomudex (Meeting abstract).

In patients (pts), the antiproliferative activity of the specific TS inhibitor Tomudex is likely to depend on factors such as *folylpolyglutamyl* *synthetase* (FPGS) and TS expression. This study investigates such potential correlations in metastatic colorectal *cancer* treated with 3 mg/m2 every 3 weeks. Pts have pre-treatment (pre-Rx) (day -1) and post-Rx (day 5) biopsies of *tumor* (CT-guided), and normal rectal/colonic (via colostomy) mucosa. Pre-Rx tissue analyses include levels of FPGS and TS mRNA (rt-PCR), and immunohistochemistry (IHC...
... and TS (IHC). Drug and deoxyuridine levels are measured in plasma. Data from the first 7 pts show that TS/beta-actin mRNA ratios in *tumor* range from 2-17, while those in large bowel range from 3-11. FPGS/beta-actin mRNA ratios in *tumor* ranged from 16-560, compared to 26-368 in bowel. Two thirds of tumors stained positive for p53. Tomudex levels on day 5 were 0.22-0.78 nmol/g in *tumor* and 0.06-0.2 nmol/g in bowel. High *tumor* /plasma and bowel/plasma drug ratios (90 and 70 respectively) were seen on day 5. To date, 4 out of 7 pts have shown disease...

7/3,K/8 (Item 2 from file: 159)

DIALOG(R)File 159:Cancerlit

01408674 98641132

A pharmacodynamic (PD) study of the thymidylate synthase (TS) inhibitor Tomudex in advanced colorectal *cancer* (CRC) (Meeting abstract).

Farrugia D; Cunningham D; Danenberg P; Danenberg K; Metzger R; Mitchell F ; MacVicar D; McCarthy K; Aherne GW; Norman A; Jackman AL
Inst. of Cancer Res., and Royal Marsden Trust, Surrey, UK

Proc Annu Meet Am Assoc Cancer Res; 38 1997 ISSN 0197-016X
Languages: ENGLISH
Document Type: MEETING ABSTRACTS
Record type: Completed

A pharmacodynamic (PD) study of the thymidylate synthase (TS) inhibitor Tomudex in advanced colorectal *cancer* (CRC) (Meeting abstract).

In pre-clinical models, activity of Tomudex depends on several factors including expression of *folylpolyglutamyl* *synthetase* (FPGS) and TS. Patients (pts) with metastatic CRC on Tomudex (3 mg/m2 q3w), have pre- (day -1) and post-treatment (day 5) *tumor* and normal rectal/colonic biopsies, with serial blood sampling. Tissue measurements include pre-treatment levels of FPGS and TS mRNA (rt-PCR), TS protein and...

... with fluorimetric detection), a PD marker for TS inhibition. Early data (7 pts) show an 8 and 4-fold variation in TS mRNA levels in *tumor* (TS/beta-actin ratios 2-17), and bowel (range 3-11) respectively. *Tumor* FPGS mRNA varied 35-fold (FPGS/beta-actin ratios 16-560) compared to 14-fold (26-368) in bowel. Around 60% of tumors were p53 positive. Tomudex levels in *tumor* and bowel on day 5 varied 4-fold (0.22-0.78 nmol/g) and 3-fold (0.06-0.2 nmol/g) respectively. Day 5 *tumor*/plasma drug ratios were high (approx 90-fold). Plasma dUrd rose 1.5 to 6-fold on day 1 but returned to pre-treatment levels...

7/3,K/9 (Item 3 from file: 159)
DIALOG(R)File 159:Cancerlit
(c) format only 2001 Dialog Corporation. All rts. reserv.

01316773 97600412
Tomudex: minimal activity in previously treated epithelial ovarian *cancer*. A gynecologic oncology group (GOG) study (Meeting abstract).
Muggia F; Blessing J; Homesley H; Sorosky JI
GOG Statistical Office, Buffalo, NY 15263
Proc Annu Meet Am Soc Clin Oncol; 15 1996 ISSN 0732-183X
Languages: ENGLISH
Document Type: MEETING ABSTRACTS
Record type: Completed

Tomudex: minimal activity in previously treated epithelial ovarian *cancer*. A gynecologic oncology group (GOG) study (Meeting abstract).
The thymidylate synthase (TS) inhibitor Tomudex (ZD1694) is a quinazoline derivative and excellent substrate of *folylpolyglutamyl* *synthetase* showing activity against a variety of solid tumors during phase I and II trials. GOG protocol 146B (Phase II epithelial ovarian *cancer* platinum-sensitive series) consisted of tomudex 3.0 mg/m2 iv every 3 weeks in patients failing one paclitaxel and/or one platinum-containing regimen ...

...and 2 patients, respectively. Although the objective response rates were insufficient to pursue further patient entry, tomudex does have some antitumor activity against epithelial ovarian *cancer*. Additional studies might be considered if TS expression or other biologic determinants should in the future allow selection of patients with a higher probability of...
?ds

Set	Items	Description
S1	0	(FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (ANTIFOLATE (W) DRUG)
S2	0	(FOLYPOLYGLUTAMYL (W) SYNTHETASE) AND (CANCER OR TUMOR OR TUMOUR OR NEOPLASTIC)
S3	0	(FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (ANTIFOLATE (W) DRUG)
S4	15	(FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (CANCER OR TUMOR OR TUMOUR OR NEOPLASTIC)
S5	2	S4 AND (VECTOR)
S6	1	RD (unique items)
S7	9	RD S4 (unique items)

?s (folylpolyglutamyl (w) synthetase) and (gene or cDNA)

	23	FOLYLPOLYGLUTAMYL
	30952	SYNTHETASE
	18	FOLYLPOLYGLUTAMYL(W)SYNTHETASE
	720524	GENE
	101217	CDNA
S8	5	(FOLYLPOLYGLUTAMYL (W) SYNTHETASE) AND (GENE OR CDNA)

?rd
...completed examining records

S9	3	RD (unique items)

?t s9/3,k/all

9/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10806665 99341974 PMID: 10413425
***Folylpolyglutamyl* *synthetase* *gene* transfer and glioma antifolate sensitivity in culture and in vivo.**
Aghi M; Kramm CM; Breakefield XO
Department of Neurology, Massachusetts General Hospital, Boston, MA, USA.
Journal of the National Cancer Institute (UNITED STATES) Jul 21 1999, 91 (14) p1233-41, ISSN 0027-8874 Journal Code: J9J

Contract/Grant No.: P3 69246, CA, NCI
Comment in J Natl Cancer Inst. 1999 Dec 1;91(23) 2047-50; Comment in J Natl Cancer Inst. 1999 Jul 21;91(14):1178-9
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

***Folylpolyglutamyl* *synthetase* *gene* transfer and glioma antifolate sensitivity in culture and in vivo.**
... against slow-growing tumors and are toxic to actively replicating cells in normal tissues. These drugs are converted intracellularly into polyglutamate derivatives by the enzyme *folylpolyglutamyl* *synthetase* (FPGS). Because tumors with high expression of FPGS often respond to nontoxic antifolate doses, we investigated whether augmenting tumoral FPGS activity by *gene* delivery would enhance tumoral antifolate sensitivity. METHODS: 9L rat gliosarcoma cells were stably transfected with a human FPGS complementary DNA (*cDNA*), producing 9L/FPGS cells. The sensitivity of these cells to the antifolates methotrexate and edatrexate was measured in culture and in subcutaneous tumors, as was...

... glioma cell lines, including one with high pre-existing FPGS activity, and in canine and human glioblastoma cell lines transduced with a vector bearing FPGS *cDNA*. CONCLUSIONS: FPGS *gene* delivery enhances the antifolate sensitivity of several glioma cell lines and merits further evaluation as a therapeutic strategy.
Descriptors: Aminopterin--analogs and derivatives--AA; *Antimetabolites, Antineoplastic--pharmacology--PD; *Folic Acid Antagonists--pharmacology--PD ; **Gene* Therapy--methods--MT; **Gene* Transfer Techniques; *Methotrexate --pharmacology--PD; *Neoplasms--therapy--TH; *Peptide Synthases--genetics --GE

9/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10770844 20048020 PMID: 10580033
Re: *Folylpolyglutamyl* *synthetase* *gene* transfer and glioma antifolate sensitivity in culture and in vivo.
Jansen G; Peters GJ; Pinedo HM; Priest DG; Assaraf YG
Journal of the National Cancer Institute (UNITED STATES) Dec 1 1999, 91 (23) p2047-50, ISSN 0027-8874 Journal Code: J9J
Comment on J Natl Cancer Inst. 1999 Jul 21;91(14) 1178-9; Comment on J Natl Cancer Inst. 1999 Jul 21;91(14):1233-41
Languages: ENGLISH
Document type: Comment; Letter
Record type: Completed

Re: *Folylpolyglutamyl* *synthetase* *gene* transfer and glioma antifolate sensitivity in culture and in vivo.
Descriptors: Antimetabolites, Antineoplastic--therapeutic use--TU; *Enzyme Inhibitors--therapeutic use--TU; *Folic Acid Antagonists --therapeutic use--TU; **Gene* Therapy; *Glioma--therapy--TH; *Peptide Synthases--genetics--GE; *Gene* Transfer Techniques; Glioma--enzymology--EN ; Tumor Cells, Cultured

9/3,K/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04067056 83171874 PMID: 6687641
Complementation mapping in microcell hybrids: localization of Fpgs and Ak-1 on Mus musculus chromosome 2.
Fournier RE; Moran RG
Somatic cell genetics (UNITED STATES) Jan 1983, 9 (1) p69-84, ISSN 0098-0366 Journal Code: VAJ
Contract/Grant No.: CA27605, CA, NCI; GM26449, GM, NIGMS